

Claims

1. An osteogenic device for implantation in a mammal, said device comprising:

a biocompatible, in vivo biodegradable matrix defining pores of a dimension sufficient to permit influx, proliferation and differentiation of migratory progenitor cells from the body of said mammal; and

a protein, produced by expression of recombinant DNA in a host cell, comprising one or more polypeptide chains, each of which has an amino acid sequence sufficiently duplicative of the sequence of COP-5 or COP-7 such that said protein is capable of inducing endochondral bone formation in association with said matrix when implanted in a mammal.

2. A device for implantation in a mammal, said device comprising:

a biocompatible, in vivo biodegradable matrix defining pores of a dimension sufficient to permit influx, proliferation and differentiation of migratory progenitor cells from the body of said mammal; and

a protein, produced by expression of recombinant DNA in a host cell, comprising one or more polypeptide chains, each of which has less than about 200 amino acids, in a sequence sufficiently duplicative of the sequence of

COP-5 or COP-7 such that said protein is capable of inducing cartilage formation in association with said matrix when implanted in a mammal.

3. The device of claim 1 or 2 wherein the sequence comprises:

| | | | | |
|--|-------------------------|-----------------|----|-----|
| 10 | 20 | 30 | 40 | 50 |
| CXXXXLXVXF | DGXWXXXPXGXXAXYCXGXCXXP | XOOOOOXXXXNHAXX | | |
| 60 | 70 | 80 | 90 | 100 |
| QXXVXXXNXXXXXPXXCCXPXXXXXXLXXXXXXVXLXXYXXMXVXXCX | | | | |

wherein each X independently represents an amino acid.

4. The device of claim 1 or 2 wherein the sequence comprises:

| | | | | |
|---|-------------------------|-----------------|----|-----|
| 10 | 20 | 30 | 40 | 50 |
| LXVXF | DGXWXXXPXGXXAXYCXGXCXXP | XOOOOOXXXXNHAXX | | |
| 60 | 70 | 80 | 90 | 100 |
| QXXVXXXNXXXXPXXCCXPXXXXXXLXXXXXXVXLXXYXXMXVXXCX | | | | |

wherein each X independently represents an amino acid.

5. The device of claim 1 or 2 wherein the sequence comprises:

| | | | | |
|----------------|-------------------------------------|-----------------|---------------|----------------|
| 10 | 20 | 30 | 40 | 50 |
| CKRHPLYVDFR | DVGWN | DWIVAPP | GYHAFYCHGECPF | PLADHLNSTNHAIV |
| RRS K S S L | QE VIS E FD Y | E A AY MPESMKAS | VI | |
| KE F E K I | DN L | N S Q | ITK F P | TL |
| Q A S K | | | | |
| 60 | 70 | 80 | 90 | 100 |
| QTLVNSVNPGKIP | KACCVPTELSAISMLYLDENENV | VULKNYQDMVVEGC | GCR | |
| SI HAI SEQV EP | A EQMNSLAI FFNDQDK I RK EE T DA H H | | | |
| RF T S | K DPV V Y N S | H RN RS | | |
| N S | K | P | E | |

wherein, in each position where more than one amino acid is shown, any one of the amino acids shown may be in that position.

6. The device of claim 1 or 2 wherein the sequence comprises:

| | | | | |
|---|--------------------|------------------|----|-----|
| 10 | 20 | 30 | 40 | 50 |
| LYVDFRDVGWNDWIVAPPGYHAFYCHGECPFPLADHLNSTNHAIV | | | | |
| K S S L | QE VIS E FD Y | E A AY MPESMKAS | VI | |
| F E K I | DN L N S | Q ITK F P | TL | |
| A S | K | | | |
| 60 | 70 | 80 | 90 | 100 |
| QTLVNSVPNGKIPKACCVPTELSAISMLYLDENENVLKNYQDMVVEGCGCR | | | | |
| SI HAI SEQV EP | A EQMNSLAI FFNDQDK | I RK EE T DA H H | | |
| RF T S | K DPV V Y N S | H RN | RS | |
| N S | | K | P | E |

wherein, in each position where more than one amino acid is shown, any one of the amino acids shown may be in that position.

7. The device of claim 1 or 2 wherein the sequence comprises:

Vg1 1 10 20 30 40
 CKKRHLVVEFK-DVGWQNWVIAAPQGYMANCYGECPPYLTE
 50 60 70
 ILNGSN--H-AIQLTLVHSIEPED-IPLPCCVPTKMSP
 80 90 100
 ISMLFYDNNNDNVVLRHYENMAVDECGR

8. The device of claim 1 or 2 wherein the sequence comprises:

DPP 1 10 20 30 40
CRRHSLYVDFS-DVGWDDWIVAPLGYDAYYCHGKCPFPLAD
50 60 70
HFNSTN--H-AVVQTLVNNNNPGK-VPKACCVPQLDS
80 90 100
VAMLYLNDQSTVVLKNYQEMTVVGCGCR

9. The device of claim 1 or 2 wherein the sequence comprises:

1 10 20 30 40
OP1 LYVSFR-DLGWQDWIIAPEGYAAYYCEGECAFPLNS
50 60 70
YMNATN--H-AIVQTLVHFINPET-VPKPCCAPTQLNA
80 90 100
ISVLYFDDSSNVILKKYRNVMVRACGCH

10. The device of claim 1 or 2 wherein the sequence comprises:

-5
HQRQA

1 10 20 30 40
OPL CKKHELYVSFR-DLGWQDWIIAPEGYAAYYCEGECAFPLNS
50 60 70
YMNATN--H-AIVQTLVHFINPET-VPKPCCAPSQLNA
80 90 100
ISVLYFDDSSNVILKKYRNMVVRACGCH

11. The device of claim 1 or 2 wherein the sequence comprises:

1 10 20 30 40
CBMP-2a CKRHPLYVDFS-DVGWNDWIVAPPGYHAFYCHGECPFPLAD
50 60 70
HLNSTN--H-AIVQTLVNSVNS-K-IPKACCVPTELSA
80 90 100
ISMLYLDENEKVVLKNYQDMVVEGCGCR

12. The device of claim 1 or 2 wherein the sequence comprises:

1 10 20 30 40
CBMP-2b CRRHSLYVDFS-DVGWNDWIVAPPGYQAFYCHGDCPFPLAD
50 60 70
HLNSTN--H-AIVQTLVNSVNS-S-IPKACCVPTELSA
80 90 100
ISMLYLDEYDKVVLKNYQEMVVEGCGCR

13. The device of claim 1 or 2 wherein the sequence comprises:

1 10 20 30 40
CBMP-3 CARRYLKVDFA-DIGWSEWIISPKSFDAYYCSGACQFPMPK
50 60 70
SLKPSN--H-ATIQSIVRAVGVVPGIPEPCCVPEKMSS
80 90 100
LSILFFDENKNVVLKVYPNMTVESACR

14. The device of claim 1 or 2 wherein the sequence comprises:

COP1 1 10 20 30 40
 LYVDFQRDVWDDWIAPVDFDAYYCSGACQFPSAD
 50 60 70
HFNSTN--H-AVVQTLVNNMNPKG-VPKPCCVPTELSA
 80 90 100
ISMLYLDENSTVVLKNYQEMTVVGCGCR

15. The device of claim 1 or 2 wherein the sequence comprises:

COP3 1 10 20 30 40
 LYVDFQRDVWDDWIVAPPGYQAFYCSGACQFPSAD
 50 60 70
HFNSTN--H-AVVQTLVNNMNPKG-VPKPCCVPTELSA
 80 90 100
ISMLYLDENEKVVALKNYQEMVVEGCGCR

16. The device of claim 1 or 2 wherein the sequence comprises:

COP4 1 10 20 30 40
 LYVDFS-DVGWDDWIVAPPGYQAFYCSGACQFPSAD
 50 60 70
HFNSTN--H-AVVQTLVNNMNPKG-VPKPCCVPTELSA
 80 90 100
ISMLYLDENEKVVALKNYQEMVVEGCGCR

17. The device of claim 1 or 2 wherein the sequence comprises:

COP5 1 10 20 30 40
 LYVDFS-DVGWDDWIVAPPGYQAFYCHGECPFPLAD
 50 60 70
HFNSTN--H-AVVQTLVNSVNSKI--PKACCVPTELSA
 80 90 100
ISMLYLDENEKVVALKNYQEMVVEGCGCR

18. The device of claim 1 or 2 wherein the sequence comprises:

COP7 1 10 20 30 40
 LYVDFS-DVGWNDWIVAPPGYHAFYCHGECPFPLAD
 50 60 70
HLNSTN--H-AVVQTLVNSVNSKI--PKACCVPTELSA
 80 90 100
ISMLYLDENEKVVALKNYQEMVVEGCGCR

19. The device of claim 1 or 2 wherein the sequence comprises:

10
PKHHSQRARKKNKN
COP16 1 10 20 30 40
CRRHSLYVDFS-DVGWNDWIVAPPGYQAFYCHGECPFPLAD
50 60 70
HFNSTN--H-AVVQTLVNSVNSKI--PKACCVPTELSA
80 90 100
ISMLYLDENEKVVLKNYQEMVVEGCGCR

20. The device of claim 1 or 2 wherein the osteogenics protein comprises a pair of separate polypeptide chains.

21. Osteogenic protein, produced by expression of recombinant DNA in a host cell, capable of inducing endochondral bone formation in association with a matrix when implanted in a mammal.

22. A protein, produced by expression of recombinant DNA in a host cell, comprising one or more polypeptide chains less than about 200 amino acids long in a sequence sufficiently duplicative of the sequence of COP-5 or COP-7 such that said protein is capable of inducing cartilage formation in association with a matrix when implanted in a mammal.

23. The osteogenic protein of claim 21 having an apparent molecular weight of about 30 kD when oxidized as determined by comparison to molecular weight standards in SDS-polyacrylamide gel.

24. The osteogenic protein of claim 23 further characterized by being glycosylated.

25. The osteogenic protein of claim 21 having an apparent molecular weight of about 27 kD as determined by comparison to molecular weight standards in SDS-polyacrylamide gel electrophoresis.

26. The protein of claim 22 or 25 further characterized by being unglycosylated.

27. The protein of claim 21 or 22 comprising a pair of separate polypeptide chains.

28. The protein of claim 21 or 22 comprising the amino acid sequences:

10 20 30 40 50
CXXXXLXVXFDXGWWXXXPXXGXXAXYCXGXCXXPXXXXXXNHA^{XX}
60 70 80 90 100
QXXVXXXNXXXXPXXCCXPXXXXXXXXXXXXXXVXLXXYXXMXVXXCX^{CX}

wherein each X independently represents an amino acid.

29. The protein of claim 21 or 22 comprising the amino acid sequences:

10 20 30 40 50
LXVXFDXGWWXXXPXXGXXAXYCXGXCXXPXXXXXXNHA^{XX}
60 70 80 90 100
QXXVXXXNXXXXPXXCCXPXXXXXXXXXXXXXXVXLXXYXXMXVXXCX^{CX}
wherein each X independently represents an amino acid.

30. The protein of claim 21 or 22 comprising the amino acid sequences:

| | | | | |
|---|---------------|-----------------|---------|-----|
| 10 | 20 | 30 | 40 | 50 |
| CKRHPLYVDFRDVGWNDWIVAPPYHAFYCHGECPPFLADHLNSTNHAI | | | | |
| RRRS K S S L | QE VIS E FD Y | E A AY MPESMKAS | | VI |
| KE F E K I | DN L | N S Q | ITK F P | TL |
| Q A S K | | | | |
| 60 | 70 | 80 | 90 | 100 |
| QTLVNSVNPKGKIPKACCVPTELSAISMLYLDENENVVLKNYQDMVVEGCCGR | | | | |
| SI HAI SEQV EP A EQMNSLAI FFNDQDK I RK EE T DA H H | | | | |
| RF T S K DPV V Y N S H RN RS | | | | |
| N S K P E | | | | |

wherein, in each position where more than one amino acid is shown, any one of the amino acids shown may be in that position.

31. The protein of claim 21 or 22 comprising the amino acid sequences:

| | | | | |
|---|---------------|-----------------|---------|-----|
| 10 | 20 | 30 | 40 | 50 |
| LYVDFRDVGWNDWIVAPPYHAFYCHGECPPFLADHLNSTNHAI | | | | |
| K S S L | QE VIS E FD Y | E A AY MPESMKAS | | VI |
| F E K I | DN L | N S Q | ITK F P | TL |
| A S K | | | | |
| 60 | 70 | 80 | 90 | 100 |
| QTLVNSVNPKGKIPKACCVPTELSAISMLYLDENENVVLKNYQDMVVEGCCGR | | | | |
| SI HAI SEQV EP A EQMNSLAI FFNDQDK I RK EE T DA H H | | | | |
| RF T S K DPV V Y N S H RN RS | | | | |
| N S K P E | | | | |

wherein, in each position where more than one amino acid is shown, any one of the amino acids shown may be in that position.

32. The protein of claim 21 or 22 comprising the amino acid sequences:

| | | | | |
|-----|---|----|-----|----|
| 1 | 10 | 20 | 30 | 40 |
| Vgl | CKKRHLYVEFK-DVGWQNWIAPQGYMANCYGECPYPLTE | | | |
| | 50 | 60 | 70 | |
| | ILNGSN--H-AILQTLVHSIEPED-IPLPCCVPTKMSP | | | |
| | 80 | 90 | 100 | |
| | ISMLFYDNNNDNVVLRHYENMAVDEC GCR | | | |

33. The protein of claim 21 or 22 comprising the amino acid sequences:

DPP 1 10 20 30 40
CRRHSLYVDFS-DVGWDDWIVAPLGYDAYYCHGKCPFPLAD
 50 60 70
HFNSTN--H-AIVQTLVNNNNPGK-VPKACCVPTQLDS
 80 90 100
VAMLYLNDQSTVVLKNYQEMTVVGCGCR

34. The protein of claim 21 or 22 comprising the amino acid sequence:

OPI 1 10 20 30 40
LYVSFR-DLGWQDWIIAPEGYAAYYCEGECAFPLNS
 50 60 70
YMNATN--H-AIVQTLVHFINPET-VPKPCCAPTQLNA
 80 90 100
ISVLYFDDSSNVILKKYRNMVVRACGCH

35. The protein of claim 21 or 22 comprising the amino acid sequences:

OPI 1 10 20 30 40
CKKHELYVSFR-DLGWQDWIIAPEGYAAYYCEGECAFPLNS
 50 60 70 -5
YMNATN--H-AIVQTLVHFINPET-VPKPCCAPTQLNA
 80 90 100
ISVLYFDDSSNVILKKYRNMVVRACGCH

36. The protein of claim 21 or 22 comprising the amino acid sequences:

CMP-2a 1 10 20 30 40
CKRHPLYVDFS-DVGWNDWIVAPPGYHAFYCHGECPFPLAD
 50 60 70
HLNSTN--H-AIVQTLVNSVNS-K-IPKACCVPTELSA
 80 90 100
ISMLYLDENEKVVLKNYQDMVVVEGCGCR

37. The protein of claim 21 or 22 comprising the amino acid sequences:

| | | | | | |
|---------|---|----|-----|----|----|
| CBMP-2b | 1 | 10 | 20 | 30 | 40 |
| | CRRHSLYVDFS-DVGWNDWIVAPPQYQAFYCHGDCPFPLAD | | | | |
| | 50 | 60 | 70 | | |
| | HLNSTN--H-AIVQTLVNSVNS-S-IPKACCVPTELSA | | | | |
| | 80 | 90 | 100 | | |
| | ISMLYLDEYDKVVLKNYQEMVVEGCGCR | | | | |

38. The protein of claim 21 or 22 comprising the amino acid sequences:

| | | | | | |
|--------|---|----|-----|----|----|
| CBMP-3 | 1 | 10 | 20 | 30 | 40 |
| | CARRYLKVDFA-DIGWSEWIISPKSFDAYYCSGACQFPMPK | | | | |
| | 50 | 60 | 70 | | |
| | SLKPSN--H-ATIQSIVRAVGVPGIPEPCCVPEKMSS | | | | |
| | 80 | 90 | 100 | | |
| | LSILFFDENKNVVLKVYPNMTVESACR | | | | |

39. The protein of claim 21 or 22 comprising the amino acid sequences:

| | | | | | |
|------|--|----|-----|----|----|
| COP1 | 1 | 10 | 20 | 30 | 40 |
| | LYVDFQRDVWDDWIIAPVDFDAYYCSGACQFPSAD | | | | |
| | 50 | 60 | 70 | | |
| | HFNSTN--H-AVVQTLVNNMNPKG-VPKPCCVPTELSA | | | | |
| | 80 | 90 | 100 | | |
| | ISMLYLDENSTVVLKNYQEMTVVGCGR | | | | |

40. The protein of claim 21 or 22 comprising the amino acid sequences:

| | | | | | |
|------|--|----|-----|----|----|
| COP3 | 1 | 10 | 20 | 30 | 40 |
| | LYVDFQRDVWDDWIVAPPQYQAFYCSGACQFPSAD | | | | |
| | 50 | 60 | 70 | | |
| | HFNSTN--H-AVVQTLVNNMNPKG-VPKPCCVPTELSA | | | | |
| | 80 | 90 | 100 | | |
| | ISMLYLDENEKVVVLKNYQEMVVEGCGCR | | | | |

41. The protein of claim 21 or 22 comprising the amino acid sequences:

| | | | | | |
|------|--|----|-----|----|----|
| COP4 | 1 | 10 | 20 | 30 | 40 |
| | LYVDFS-DVGWDDWIVAPPQYQAFYCSGACQFPSAD | | | | |
| | 50 | 60 | 70 | | |
| | HFNSTN--H-AVVQTLVNNMNPKG-VPKPCCVPTELSA | | | | |
| | 80 | 90 | 100 | | |
| | ISMLYLDENEKVVVLKNYQEMVVEGCGCR | | | | |

42. The protein of claim 21 or 22 comprising the amino acid sequences:

COP5 1 10 20 30 40
 LYVDFS-DVGWDDWIVAPPGYQAFYCHGECPFPLAD
 50 60 70
 HFNSTN--H-AVVQTLVNSVNSKI--PKACCVPTELSA
 80 90 100
 ISMLYLDENEKVVVLKNYQEMVVEGCGCR

43. The protein of claim 21 or 22 comprising the amino acid sequences:

COP7 1 10 20 30 40
 LYVDFS-DVGWNDWIVAPPGYHAFYCHGECPFPLAD
 50 60 70
 HLNSTN--H-AVVQTLVNSVNSKI--PKACCVPTELSA
 80 90 100
 ISMLYLDENEKVVVLKNYQEMVVEGCGCR

44. The protein of claim 21 or 22 comprising the amino acid sequences:

COP16 1 10 20 30 40
 CRRHSLYVDFS-DVGWNDWIVAPPGYQAFYCHGECPFPLAD
 50 60 70
 -10
 PKHHSSRARKKNKN
 HFNSTN--H-AVVQTLVNSVNSKI--PKACCVPTELSA
 80 90 100
 ISMLYLDENEKVVVLKNYQEMVVEGCGCR

45. The protein of claim 21 or 22 comprising the product of expression of a DNA in a procaryotic cell.

46. A DNA sequence encoding an amino acid sequence sufficiently duplicative of that of the sequence encoded by the gene of Figure 1A such that said encoded sequence induces bone or cartilage formation when implanted in a mammal in association with a matrix.

47. The DNA of claim 46 encoding the same amino acid sequence as the gene set forth in Figure 1A.

48. The DNA sequence of claim 46 encoding:

1 10 20 30 40
OPI LYVSFR-DLGWQDWIIAPEGYAAYYCEGECAFPLNS
 50 60 70
 YMNATN--H-AIVQTLVHFINPET-VPKPCCAPTQLNA
 80 90 100
 ISVLYFDDSSNVILKKYRNRMVVVRACGCH

49. The DNA sequence of claim 46 encoding:

1 10 20 30 40 -5
OPI. CKKHELYVSFR-DLGWQDWIIAPEGYAAYYCEGECAFPLNS
 50 60 70 HQRQA
 YMNATN--H-AIVQTLVHFINPET-VPKPCCAPTQLNA
 80 90 100
 ISVLYFDDSSNVILKKYRNRMVVVRACGCH

50. A cell line engineered to express the protein of claim 21 or 22.

51. The protein of claim 21 having a half maximum bone forming activity of about 20 - 25 ng per 25 mg of implant.

52. A biocompatible, in vivo biodegradable deglycosylated collagenous matrix defining pores of dimensions sufficient to permit influx, proliferation, and differentiation of migratory progenitor cells from the body of a mammal.

53. The matrix of claim 52 comprising close-packed particulate matter having a particle size within the range of 70-850 mm.

54. The matrix of claim 53 wherein said particulate matter has a particle size within the range of 70-420 mm.

55. The matrix of claim 52 defining a shape to span a non-union fracture in said mammal.

56. The matrix of claim 52 comprising demineralized, protein-extracted, deglycosylated, particulate xenogenic bone.

57. The matrix of claim 52 comprising a material selected from the group consisting of hydroxyapatite, tricalcium phosphate, polymers comprising lactic acid monomer units, polymers comprising glycolic acid monomer units, demineralized, guanidine-extracted, deglycosylated xenogenic bone, and mixtures thereof.

58. An osteogenic device for implantation in a mammal, said device comprising:

a biocompatible, in vivo biodegradable matrix defining pores of a dimension sufficient to permit influx, proliferation and differentiation of migratory progenitor cells from the body of said mammal; and

substantially pure osteogenic protein capable of inducing endochondral bone formation in said mammal disposed in said matrix and accessible to said cells.

59. The device of claim 1, 2, or 58 wherein said matrix comprises close-packed particulate matter having a particle size within the range of 70-850 mm.

60. The device of claim 1, 2, or 58 wherein said particulate matter has a particle size within the range of 70-420 mm.

61. The device of claim 1, 2, or 58 wherein said matrix comprises demineralized, protein-extracted, particulate, allogenic bone.

62. The device of claim 1, 2, or 58 wherein said matrix comprises a material selected from the group consisting of collagen, hydroxyapatite, tricalcium phosphate, polymers comprising lactic acid monomer units, polymers comprising glycolic acid monomer units, demineralized, guanidine-extracted allogenic bone, and mixtures thereof.

63. The device of claim 1, 2, or 58 wherein said matrix is shaped to span a non-union fracture in said mammal.

64. The device of claim 1, 2, or 58 disposed within the marrow cavity of allogenic bone.

65. The device of claim 1, 2, or 58 wherein said matrix comprises demineralized, protein extracted, particulate, deglycosylated xenogeneic bone.

66. The device of claim 65 wherein said matrix is treated with a protease.

67. The device of claim 58 wherein said osteogenic protein is unglycosylated. ^{ns}

68. The device of claim 67 wherein said osteogenic protein has an apparent molecular weight of about 27 kD when oxidized as determined by comparison to molecular weight standards in SDS-polyacrylamide gel electrophoresis.

69. The device of claim 58 wherein said osteogenic protein is glycosylated. ^{rs}

70. The device of claim 69 wherein said osteogenic protein has an apparent molecular weight of about 30 kD when oxidized as determined by comparison to molecular weight standards in SDS-polyacrylamide gel electrophoresis. ^{rs}

71. The device of claim 58 wherein said osteogenic protein comprises a pair of polypeptide chains.

72. The device of claim 71 wherein one chain of said pair of polypeptide chains has an apparent molecular weight of about 14 kD and the other has an apparent molecular weight of about 16 kD, both as determined after reduction by comparison to molecular weight standards in SDS-polyacrylamide gel electrophoresis. ^{rs}

73. The device of claim 71 wherein one chain of said pair of polypeptide chains has an apparent molecular weight of about 16 kD and the other has an apparent molecular weight of about 18 kD, both as determined after reduction by comparison to molecular weight standards in SDS-polyacrylamide gel electrophoresis.

74. The device of claim 58 wherein said osteogenic protein has the approximate amino acid composition set forth below:

| Amino acid <u>residue</u> | Rel. no. <u>res./molec.</u> | Amino acid <u>residue</u> | Rel. no. <u>res./molec.</u> |
|------------------------------|--------------------------------|------------------------------|--------------------------------|
| Aspartic acid/ | 22 | Tyrosine | 11 |
| Asparagine | | Valine | 14 |
| Glutamic acid/ | 24 | Methionine | 3 |
| Glutamine | | Cysteine | 16 |
| Serine | 24 | Isoleucine | 15 |
| Glycine | 29 | Leucine | 15 |
| Histidine | 5 | Proline | 14 |
| Arginine | 13 | Phenylalanine | 7 |
| Threonine | 11 | Tryptophan | ND |
| Alanine | 18 | | |
| Lysine | 12 | | |

75. The device of claim 58 wherein said osteogenic protein comprises the amino acid sequence:

VPKPCCAPT

76. The device of claim 1 or 58 wherein the half maximum bone inducing activity of said protein is 0.8 to 1.0 ng per mg of said matrix.

77. A method of inducing local cartilage or bone formation in a mammal comprising the step of implanting the device of claim 1, 2, or 58 in said mammal at a locus accessible to migratory progenitor cells of said mammal.

78. A method of inducing endochondral bone formation in a mammal comprising the step of implanting the device of claim 1 or 58 in said mammal at a locus accessible to migratory progenitor cells of said mammal.

79. A method of inducing endochondral bone formation in a non-union fracture in a mammal comprising the step of implanting in the fracture in said mammal the device of claim 63.

80. Antibodies reactive with an epitope of the protein of claim 21 or 22.